



PATENT
Docket No. 13761-7064

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By: *[Signature]*

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: DeLeve, Laurie

Confirmation No.: 1401

Filing Date: February 27, 2002

Examiner: Sharareh, Shahnam J.

Serial No.: 10/086, [REDACTED]

Group Art Unit: 1617

Title: **COMPOSITION AND METHOD FOR PREVENTING AND TREATING SINUSOIDAL OBSTRUCTION SYNDROME AND RADIATION-INDUCED LIVER DISEASE**

Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

DECLARATION OF LAURIE DELEVE UNDER 37 C.F.R. § 1.132

I, Laurie DeLeve, citizen of the United States, hereby declare that:

1. I am the Laurie DeLeve who is the named inventor of the above-identified application. I also am the Laurie DeLeve who is the first author of the attached publication entitled "Sinusoidal Obstruction Syndrome (Veno-Occlusive Disease) in the Rat is Prevented by Matrix Metalloproteinase Inhibition", Gastroenterology (2003) 125:882-890. All studies reported in this publication were performed by me or under my direction and supervision.
2. The attached application reports on Applicant's discovery that sinusoidal obstruction syndrome (SOS) is caused by up-regulation of metalloproteinase enzyme in a clinically relevant animal model of the disease. Applicant also reports that inhibition of matrix metalloproteinase-9 and metalloproteinase-2 activity matrix (MMP-9 and MMP-2,

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respectively) activity. Administration of effective amounts of metal metalloproteinase inhibitors prevented the development of SOS in this animal model.

3. As noted on page 884 of the publication, 2 different MMP inhibitors were administered to the animals. One subgroup received 3 different doses of doxycycline (5, 10 and 15 mg/kg IG) twice daily from day -2 until the time of sacrifice. The second group received the MMP-2/MMP-9 inhibitor 2-[4-biphenylsulfonyl]amino]-3-phenyl-propionic acid at two different doses, namely 100 or 200 µg/hour. The drug was infused intraperitoneally using an osmotic pump via a cannula inserted into the inferior mesenteric vein from day -1 until the time of sacrifice. Control studies were performed with 2 chemically modified tetracyclines that are known weak MMP inhibitors: isochlorotetracycline, 15 mg/kg IG, were given twice daily from day -2 on.

5. On page 887 of the publication, it is reported that clinical signs of SOS in this model, e.g., ascites formation, increased liver weight, and decreased hematocrit, were completely prevented by 2-[4-biphenylsulfonyl]amino]-3-phenyl-propionic acid, and were nearly completely prevented by 15 mg/kg IG of doxycycline. What is inferred, but not explicitly stated in the publication is that lower dosages (5 and 10 mg/kg) did not prevent clinical signs of SOS in the animals.

6. I further declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: May 26, 2005



Laurie DeLeve, M.D.

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